8. Outcome of simian-human immunodeficiency virus strain 89.6p challenge following vaccination of rhesus macaques with human immunodeficiency virus Tat protein

By Silvera, Peter; Richardson, Max W.; Greenhouse, Jack; Yalley-Ogunro, Jake; Shaw, Nigel; Mirchandani, Jyotika; Khalili, Kamel; Zagury, Jean-Francois; Lewis, Mark G.; Rappaport, Jay
From Journal of Virology (2002), 76(8), 3800-3809. Language: English, Database: CAPLUS, DOI:10.1128/JVI.76.8.3800-3809.2002

The regulatory proteins Nef, Rev, and Tat of human immunodeficiency virus type 1 (HIV-1) are attractive targets for vaccine development, since induction of effective immune responses targeting these early proteins may best control virus replication. Here the authors investigated whether vaccination with biol. active Tat or inactive Tat toxoid derived from HIV-1IIIB and simian-human immunodeficiency virus (SHIV) strain 89.6p would induce protective immunity in rhesus macaques. Vaccination induced high titers of anti-Tat IgG in all immunized animals by week 7, but titers were somewhat lower in the 89.6p Tat group. Dominant B-cell epitopes mapped to the amino terminus, the basic domain, and the carboxy-terminal region. Tat-specific T-helper responses were detected in 50% of immunized animals. T-cell epitopes appeared to map within amino acids (aa) 1 to 24 and aa 37 to 66. In addn., Tat-specific gamma interferon responses were detected in CD4+ and/or CD8+ T lymphocytes in 11 of 16 immunized animals on the day of challenge. However, all animals became infected upon i.v. challenge with 30 50% minimal IDs of SHIV 89.6p, and there were no significant differences in viral loads or CD4+ T-cell counts between immunized and control animals. Thus, vaccination with HIV-1IIIB or SHIV 89.6p Tat or with Tat toxoid prepns. failed to confer protection against SHIV 89.6p infection despite robust Tat-specific humoral and cellular immune responses in some animals. Given its apparent immunogenicity, Tat may be more effective as a component of a cocktail vaccine in combination with other regulatory and/or structural proteins of HIV-1.

~61 Citings

15. Vaccination with Tat toxoid attenuates disease in simian/HIV-challenged macaques

By Pauza, C. David; Trivedi, Parul; Wallace, Marianne; Ruckwardt, Tracy J.; Le Buanec, Helene; Lu, Wei; Bizzini, Bernard; Burny, Arsene; Zagury, Daniel; Gallo, Robert C.
From Proceedings of the National Academy of Sciences of the United States of America (2000), 97(7), 3515-3519. Language: English, Database: CAPLUS, DOI:10.1073/pnas.070049797

The Tat protein is essential for HIV type 1 (HIV-1) replication and may be an important virulence factor in vivo. The authors studied the role of Tat in viral pathogenesis by immunizing rhesus macaques with chem. inactivated Tat toxoid and challenging these animals by intrarectal inoculation with the simian/human immunodeficiency virus 89.6PD. Immune animals had attenuated disease with lowered viral RNA, interferon-α, and chemokine receptor expression (CXCR4 and CCR5) on CD4+ T cells; these features of infection have been linked to in vitro effects of Tat and respond similarly to extracellular Tat protein produced during infection. Immunization with Tat toxoid inhibits key steps in viral pathogenesis and should be included in therapeutic or preventive HIV-1 vaccines.

~113 Citings

19. Tat toxoid as a component of a preventive vaccine in seronegative subjects

By Gringeri, Alessandro; Santagostino, Elena; Muca-Perja, Myrvet; Le Buanec, Helene; Bizzini, Bernard; Lachgar, Abderrhaim; Zagury, Jean-Francois; Rappaport, Jay; Burny, Arsene; Gallo, Robert C.; et al
From Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1999), 20(4), 371-375. Language: English, Database: CAPLUS, DOI:10.1097/00042560-199904010-00007

Because administration of Tat protein, the HIV-1 toxin that induces immunosuppression and apoptosis, may be deleterious to the host immune system, a chem. inactivated but nonetheless immunogenic Tat prepn., Tat toxoid, was used to immunize seroneg. individuals against Tat. In an open, controlled, phase I clin. trial, Tat toxoid turned out to be safe, well tolerated, and able to trigger a specific immune reaction. In particular, a threefold to more than 10-fold increase of circulating antibodies directed against the native Tat was obsd. after immunization in all of 5 immunized study subjects, together with a pos. reaction to delayed-type hypersensitivity (DTH) skin test with Tat toxoid in vivo and increased lymphoproliferative response to native Tat in vitro. Persistent (≥1 yr) high levels of circulating anti-Tat antibodies could prevent the Tat-induced immune suppression and, following HIV-1 exposure, allow the anti-HIV-1 cellular immune response, with its early release of protective β-chemokines, to occur leading to an increase of host resistance, i.e., protection.

~31 Citings

23. Safety and immunogenicity of HIV-1 Tat toxoid in immunocompromised HIV-1-infected patients

By Gringeri, A.; Santagostino, E.; Muca-Perja, M.; Mannucci, P. M.; Zagury, J. F.; Bizzini, B.; Lachgar, A.; Carcagno, M.; Rappaport, J.; Criscuolo, M.; et al
From Journal of Human Virology (1998), 1(4), 293-298. Language: English, Database: CAPLUS

To antagonize the deleterious effects of the HIV-1 toxin extracellular Tat on uninfected immune cells, the authors developed a new strategy of anti-HIV-1 vaccine using an inactivated but immunogenic Tat (Tat toxoid). Tat toxoid has been assayed for safety and immunogenicity in seropos. patients. The phase I vaccine clin. trial testing Tat toxoid prepn. in Seppic Isa 51 oil adjuvant was performed on 14 HIV-1-infected asymptomatic although biol. immunocompromised individuals (500-200 CD4+ cells/mm3). Following as many as 8 injections, no clin. defects were obsd. All patients exhibited an antibody (Ab) response to Tat, and some had cell-mediated immunity (CMI) as evaluated by skin test in vivo and T-cell proliferation in vitro. These results provide initial evidence of safety and potency of Tat toxoid vaccination in HIV-1-infected individuals.

~79 Citings